

We claim:

1. A method for identifying chemosensitizing compounds that reverse non P-gp/non MRP multiple drug resistance in cancer cells exhibiting non P-gp/non MRP drug resistance phenotype comprising administration of a test compound and a chemotherapeutic agent to which cancer cells are resistant and measuring cancer cell survival.
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2. A method for resensitizing non P-gp/non MRP multiple drug resistant cancer cells to treatment with chemotherapeutic agents to which cancer cells have developed resistance comprising administration of an effective amount of a chemosensitizing reversal agent and a chemotherapeutic agent.
- 15
3. The method according to claim 2 wherein the chemosensitizing reversal agent is selected from the group consisting of fumitremorgin A, fumitremorgin B and fumitremorgin C.
- 20
4. The method according to claim 2 wherein the chemotherapeutic agent used is one to which the cancer cells are resistant.
5. The method according to claim 2 wherein the chemotherapeutic agent is selected from the group consisting of mitoxantrone, doxorubicin and topotecan.
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6. The method of claim 3 wherein the chemosensitizing reversal agent is administered prior to, concurrently with, or after administration of the chemotherapeutic agent.
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7. A method for identifying chemosensitizing compounds that reverse BCRP-mediated multiple drug resistance in cancer cells which exhibit BCRP-mediated multiple drug resistance comprising administration of a test compound and a chemotherapeutic agent to which the cancer cells are resistant and measuring cancer cell survival.
- 35
8. A method for resensitizing BCRP-mediated multiple drug resistant cancer cells to treatment with chemotherapeutic agents to which cancer cells have developed resistance comprising administration of an effective amount of a chemosensitizing reversal agent and a chemotherapeutic agent.
- 40
9. The method according to claim 8 wherein the chemotherapeutic agent used is one to which the cancer cells are resistant.

10. The method according to claim 9 wherein the chemotherapeutic agent is selected from the group consisting of mitoxantrone, doxorubicin, and topotecan.

10 11. The method according to claim 8 wherein the chemosensitizing reversal agent is selected from the group consisting of fumitremorgin A, fumitremorgin B and fumitremorgin C.

15 12. The method according to claim 11 wherein the chemosensitizing reversal agent is administered prior to, concurrently with, or after administration of the chemotherapeutic agent.

20 13. A method of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance which comprises administration of an effective amount of a chemosensitizing reversal agent and a chemotherapeutic agent to which cancer cells are resistant and measuring cancer cell survival.

25 14. The method according to claim 13 wherein the chemotherapeutic agent used is one to which the cancer cells are resistant.

15. The method according to claim 13 wherein the chemotherapeutic agent is selected from the group consisting of mitoxantrone, doxorubicin, and topotecan.

30 16. The method according to claim 13 wherein the chemosensitizing reversal agent is selected from the group consisting of fumitremorgin A, fumitremorgin B and fumitremorgin C.

35 17. The method according to claim 16 wherein the chemosensitizing reversal agent is administered prior to, concurrently with, or after administration of the chemotherapeutic agent.

40 18. A method of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance which comprises administration of an effective amount of a chemosensitizing reversal agent and a chemotherapeutic agent to which the cancer cells are multiple drug resistant and measuring chemotherapeutic agent accumulations in the cell.

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19. The method according to claim 18 wherein the chemotherapeutic agent used is one to which the cancer cells are resistant.

10 20. The method according to claim 18 wherein the chemotherapeutic agent is selected from the group consisting of mitoxantrone, doxorubicin, and topotecan.

15 21. The method according to claim 18 wherein the chemotherapeutic agent is substituted by a drug surrogate.

20 22. The method according to claim 18 wherein the chemosensitizing reversing agent is selected from the group consisting of fumitremorgin A, fumitremorgin B and fumitremorgin C.

25 23. The method according to claim 22 wherein the chemosensitizing reversal agent is administered prior to, concurrently with, or after administration of the chemotherapeutic agent.

25 24. A method of determining the presence and magnitude of cancer cell BCRP or other non P-gp/non MRP resistance in cancer cells exhibiting such resistance which comprises administration of an effective amount of a chemosensitizing reversal agent and chemotherapeutic agents to resistant cancer cells from humans and measuring cancer cell survival.

30 25. The method according to claim 24 wherein the chemotherapeutic agent used is one to which the cancer cells are resistant.

26. The method according to claim 24 wherein the chemotherapeutic agent is selected from the group consisting of mitoxantrone, doxorubicin, and topotecan.

35 27. The method according to claim 24 wherein the chemosensitizing reversal agent is selected from the group consisting of fumitremorgin A, fumitremorgin B and fumitremorgin C.

40 28. The method according to claim 27 wherein the chemosensitizing reversal agent is administered prior to, concurrently with, or after administration of the chemotherapeutic agent.

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29. A method of reversing BCRP or other non P-gp/non MRP resistance to chemotherapeutic agents in a mammal which comprises administration of an effective amount of a chemosensitizing reversal agent to a mammal in need thereof having a BCRP or other non-P-gp/non MRP resistant cancer.

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30. The method according to claim 29 wherein the chemotherapeutic agent used is one to which the cancer cells are resistant.

15

31. The method according to claim 29 wherein the chemotherapeutic agent is selected from the group consisting of mitoxantrone, doxorubicin, and topotecan.

32. The method according to claim 29 wherein the chemosensitizing reversal agent is selected from the group consisting of fumitremorgin A, fumitremorgin B and fumitremorgin C.

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33. The method according to claim 32 wherein the chemosensitizing reversal agent is administered prior to, concurrently with, or after administration of the chemotherapeutic agent.

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34. A method of treatment of BCRP or other non P-gp/non MRP multiple drug resistant phenotype cancer cells which comprises administration of an effective amount of a chemosensitizing reversal agent and a chemotherapeutic agent to which the cancer is resistant.

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35. The method according to claim 34 wherein the chemotherapeutic agent used is one to which the cancer cells are resistant.

36. The method according to claim 34 wherein the chemotherapeutic agent is selected from the group consisting of mitoxantrone, doxorubicin, and topotecan.

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37. The method according to claim 34 wherein the chemosensitizing reversal agent is selected from the group consisting of fumitremorgin A, fumitremorgin B and fumitremorgin C.

5 38. The method according to claim 37 wherein the chemosensitizing reversal agent is  
administered prior to, concurrently with, or after administration of the chemotherapeutic  
agent.

10 39. The method of inhibiting efflux of a chemotherapeutic agent in a mammal in need  
thereof which comprises administration of an effective amount of a chemosensitizing  
reversal agent and a chemotherapeutic agent to which the cancer is resistant.

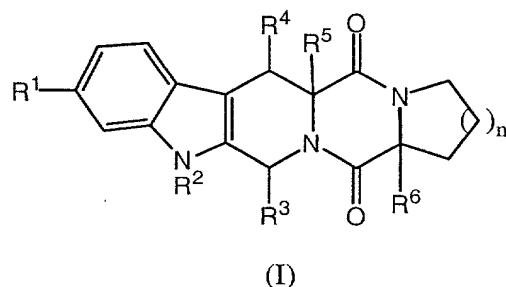
15 40. The method according to claim 39 wherein the chemotherapeutic agent used is one to  
which the cancer cells show resistance to the BCRP or other non P-gp/MRP-mediated  
phenotype.

41. The method according to claim 39 wherein the chemotherapeutic agent is selected from  
the group consisting of mitoxantrone, doxorubicin, and topotecan.

20 42. The method according to claim 39 wherein the chemosensitizing reversal agent is  
selected from the group consisting of fumitremorgin A, fumitremorgin B and  
fumitremorgin C.

25 43. The method according to claim 42 wherein the chemosensitizing reversal agent is  
administered prior to, concurrently with, or after administration of the chemotherapeutic  
agent.

## 44. A compound having the Formula (I)



(I)

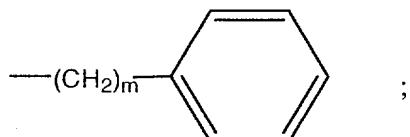
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wherein:

n is an integer of 0, 1, or 2;

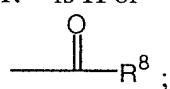
 $R^1$  is hydrogen or alkoxy of 1 to 10 carbon atoms; $R^2$  is hydrogen or alkenyl of 2 to 10 carbon atoms;

5 R<sup>3</sup> is hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms,  
R<sup>7</sup>NH(CH<sub>2</sub>)<sub>v</sub>– or

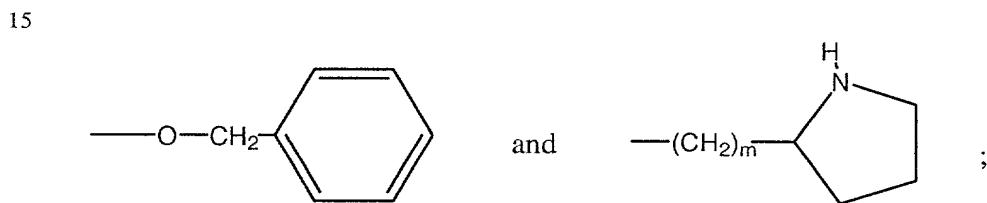


m is an integer of 1 to 6;

10 v is an integer of 1 to 4;  
R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;  
R<sup>7</sup> is H or



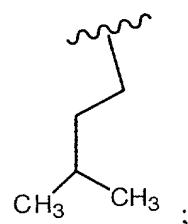
R<sup>8</sup> is selected from alkyl of 1 to 10 carbon atoms, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>H,



20 with the proviso that n is not 1 when

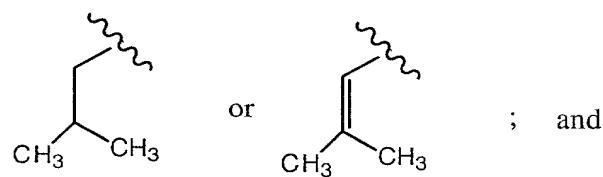
R<sup>1</sup> is H or CH<sub>3</sub>O–;

R<sup>2</sup> is H or



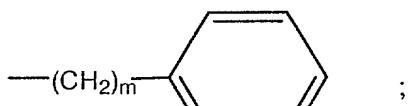
25

R<sup>3</sup> is



5 R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;  
or a pharmaceutically acceptable salt thereof.

45. A compound according to claim 44 wherein  
10 R<sup>1</sup> is hydrogen or alkoxy of 1 to 5 carbon atoms;  
R<sup>2</sup> is hydrogen or alkenyl of 2 to 6 carbon atoms;  
R<sup>3</sup> is hydrogen, alkyl of 1 to 9 carbon atoms, alkenyl of 2 to 6 carbon atoms,  
R<sup>7</sup>NH(CH<sub>2</sub>)<sub>v</sub>— or



15 m is an integer of 1 to 5;  
v is an integer of 1 to 3;  
or a pharmaceutically acceptable salt thereof.

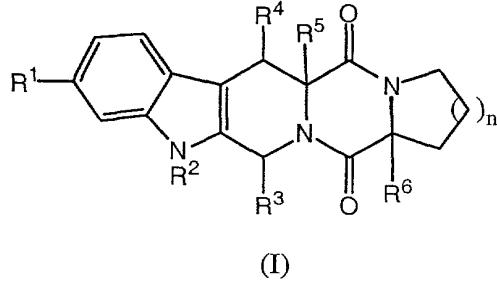
20 46. A compound according to claim 44 wherein  
R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently (R) or (S);  
or a pharmaceutically acceptable salt thereof.

25 47. A compound according to claim 44 wherein  
R<sup>1</sup> is hydrogen or CH<sub>3</sub>O-;  
R<sup>2</sup> is hydrogen or 3-methyl-2-buten-1-yl;  
R<sup>3</sup> is hydrogen or (R) or (S) 2-methylpropyl, 2-methyl-2-propenyl, nonanyl, 5-phenylpentyl, or R<sup>7</sup>NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- where R<sup>7</sup> is hydrogen, acetyl, butyryl, succinoyl, or  
30 3-(2-pyrrolidinyl)propionyl;  
R<sup>4</sup> and R<sup>5</sup> independently are (R) or (S) hydrogen;  
or a pharmaceutically acceptable salt thereof.

48. The compound of claim 44 which is selected from the group consisting of  
35 (5aS,12R,14aR)-12-isobutyl-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5,14-dione,  
(5aS,12S,14aR)-12-isobutyl-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5,14-dione,

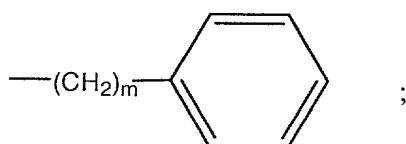
5 (5aR,12R,14aR)-12-isobutyl-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-  
pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5,14-dione,  
(5aR,12S,14aR)-12-isobutyl-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-  
pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5,14-dione,  
(6aS,13R,15aS)-13-isobutyl-1,2,3,4,6a,7,12,13,15a-nonahydro-6H,15H-  
10 pyrido[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-6H,15H-dione,  
(6aS,13S,15aS)-13-isobutyl-1,2,3,4,6a,7,12,13,15a-nonahydro-6H,15H-  
pyrido[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-6H,15H-dione,  
(6aR,13R,15aS)-13-isobutyl-1,2,3,4,6a,7,12,13,15a-nonahydro-6H,15H-  
15 pyrido[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-6H,15H-dione,  
(6aR,13S,15aS)-13-isobutyl-1,2,3,4,6a,7,12,13,15a-nonahydro-6H,15H-  
pyrido[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-6H,15H-dione,  
(6aS,13R,15aR)-13-isobutyl-1,2,3,4,6a,7,12,13,15a-nonahydro-6H,15H-  
20 pyrido[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-6H,15H-dione,  
(6aS,13S,15aR)-13-isobutyl-1,2,3,4,6a,7,12,13,15a-nonahydro-6H,15H-  
pyrido[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-6H,15H-dione,  
(6aR,13S,15aR)-13-isobutyl-1,2,3,4,6a,7,12,13,15a-nonahydro-6H,15H-  
25 pyrido[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-6H,15H-dione,  
(4aS,11R,13aS)-11-isobutyl-1,4a,5,10,11,13a-hexahydro-4H-  
azeto[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-4,13(2H)-dione,  
(4aS,11S,13aS)-11-isobutyl-1,4a,5,10,11,13a-hexahydro-4H-  
azeto[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-4,13(2H)-dione,  
(5aS,12R,14aS)-12-(5-phenylpentyl)-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-  
30 pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5,14-dione,  
(5aS,12S,14aS)-12-(5-phenylpentyl)-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-  
pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5,14-dione;  
benzyl 3-[(5aS,12R,14aS)-5,14-dioxo-2,3,5a,6,11,12,14,14a-octahydro-1H,5H-  
35 pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indol-12-yl]propylcarbamate,  
benzyl 3-[(5aS,12S,14aS)-5,14-dioxo-2,3,5a,6,11,12,14,14a-octahydro-1H,5H-  
pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indol-12-yl]propylcarbamate,  
(5aS,14aS)-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-  
40 pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5,14-dione,

5 (5aS,12S,14aS)-12-nonyl-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5,14-dione,  
10 (5aS,12R,14aS)-12-(3-aminopropyl)-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5,14-dione,  
15 (5aS,12S,14aS)-12-(3-aminopropyl)-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5,14-dione,  
N-{3-[(5aS,12S,14aS)-5,14-dioxo-2,3,5a,6,11,12,14,14a-octahydro-1H,5H-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indol-12-yl]propyl}acetamide,  
N-{3-[(5aS,12S,14aS)-5,14-dioxo-2,3,5a,6,11,12,14,14a-octahydro-1H,5H-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indol-12-yl]propyl}butanamide,  
20 4-({3-[(5aS,12S,14aS)-5,14-dioxo-2,3,5a,6,11,12,14,14a-octahydro-1H,5H-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indol-12-yl]propyl}amino)-4-oxobutanoic acid,  
25 (2S)-N-{3-[(5aS,12S,14aS)-5,14-dioxo-2,3,5a,6,11,12,14,14a-octahydro-1H,5H-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indol-12-yl]propyl}pyrrolidine-2-carboxamide and  
(5aS,12S,14aS)-9-methoxy-11-(3-methylbut-2-enyl)-12-(2-methylprop-1-enyl)-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5,14-dione or a pharmaceutically acceptable salt thereof.



30 wherein:  
n is an integer of 0, 1, or 2;  
 $R^1$  is hydrogen or alkoxy of 1 to 10 carbon atoms;  
 $R^2$  is hydrogen or alkenyl of 2 to 10 carbon atoms;  
 $R^3$  is hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms,  
35  $R^7NH(CH_2)v-$  or

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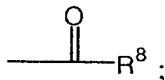


m is an integer of 1 to 6;

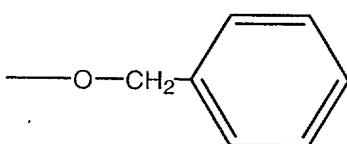
v is an integer of 1 to 4;

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

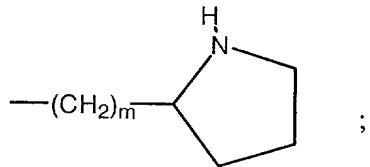
10 R<sup>7</sup> is H or



R<sup>8</sup> is selected from alkyl of 1 to 10 carbon atoms, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>H,



and

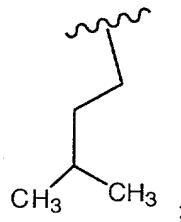


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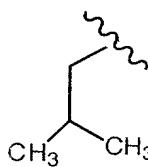
with the proviso that n is not 1 when

R<sup>1</sup> is H or CH<sub>3</sub>O-;

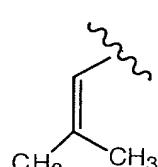
20 R<sup>2</sup> is H or



25 R<sup>3</sup> is



or



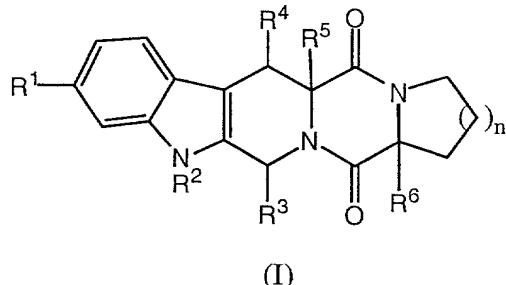
and

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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50. A method of treating multiple drug resistance in a mammal in need thereof, which comprises administering to said mammal, a chemotherapeutic agent and an effective amount of a chemosensitizing reversal agent of Formula (I)



(1)

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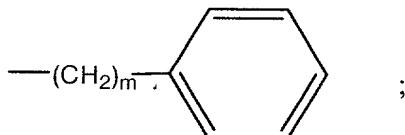
wherein:

n is an integer of 0, 1, or 2;

$R^1$  is hydrogen or alkoxy of 1 to 10 carbon atoms:

$R^2$  is hydrogen or alkenyl of 2 to 10 carbon atoms:

15  $R^3$  is hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms,  $R^7NH(CH_2)y-$  or

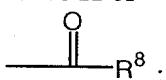


m is an integer of 1 to 6:

20 v is an integer of 1 to 4;

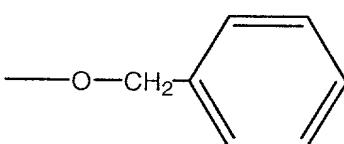
$R^4, R^5$  and  $R^6$  are hydrogen:

$R^7$  is H or

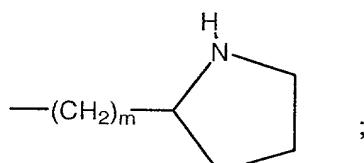


$R^8$  is selected from alkyl of 1 to 10 carbon atoms  $-(CH_2)_nCO_2H$

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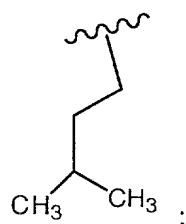
and



5 with the proviso that n is not 1 when

R<sup>1</sup> is H or CH<sub>3</sub>O-;

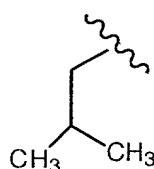
R<sup>2</sup> is H or



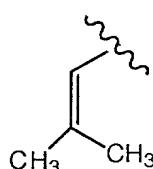
;

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R<sup>3</sup> is



or



; and

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

15 or a pharmaceutically acceptable salt thereof; said chemosensitizing reversal agent being administered in an effective amount to increase the sensitivity of the chemotherapeutic agent to the multiple drug resistant cancer.

20 51. The method of claim 50 wherein the multiple drug resistant cancer is non P-gp/non MRP.

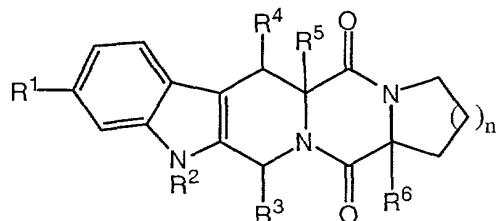
52. The method of claim 50 wherein the multiple drug resistant cancer expresses BCRP.

25

53. The method of claim 50 wherein the chemotherapeutic agent is selected from the group consisting of mitoxantrone, doxorubicin and topotecan.

30 54. The method according to claim 50 wherein the chemotherapeutic agent used is one to which the cancer cells are resistant.

55. The method according to claim 2 wherein the chemosensitizing reversal agent is a compound having the Formula (I)



(I)

5

wherein:

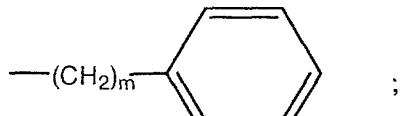
n is an integer of 0, 1, or 2;

R<sup>1</sup> is hydrogen or alkoxy of 1 to 10 carbon atoms;

10 R<sup>2</sup> is hydrogen or alkenyl of 2 to 10 carbon atoms;

R<sup>3</sup> is hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms,

R<sup>7</sup>NH(CH<sub>2</sub>)<sub>v</sub>- or

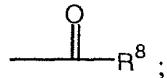


15 m is an integer of 1 to 6;

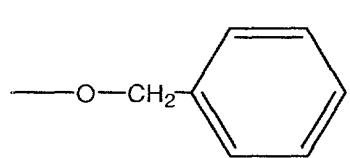
v is an integer of 1 to 4;

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

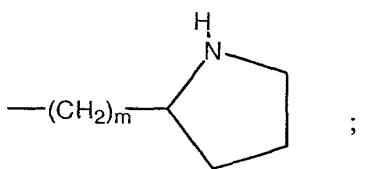
R<sup>7</sup> is H or



20 R<sup>8</sup> is selected from alkyl of 1 to 10 carbon atoms, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>H,



and

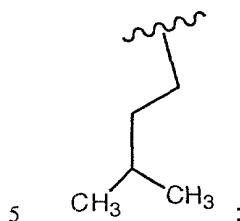


25

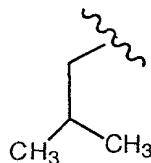
with the proviso that n is not 1 when

R<sup>1</sup> is H or CH<sub>3</sub>O-;

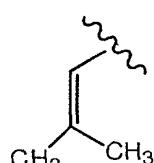
R<sup>2</sup> is H or



R<sup>3</sup> is



or



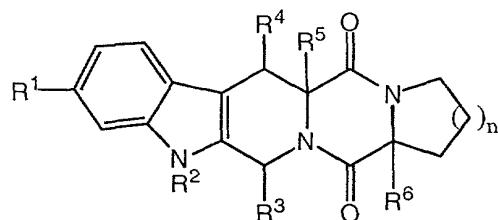
and

10

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;  
or a pharmaceutically acceptable salt thereof.

15

56. The method according to claim 8 wherein the chemosensitizing reversal agent is  
selected from a compound having the Formula (I)



(I)

wherein:

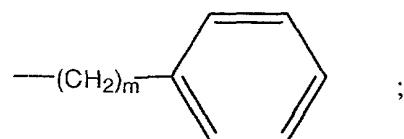
n is an integer of 0, 1, or 2;

20 R<sup>1</sup> is hydrogen or alkoxy of 1 to 10 carbon atoms;

R<sup>2</sup> is hydrogen or alkenyl of 2 to 10 carbon atoms;

R<sup>3</sup> is hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms,

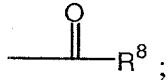
R<sup>7</sup>NH(CH<sub>2</sub>)<sub>v</sub>- or



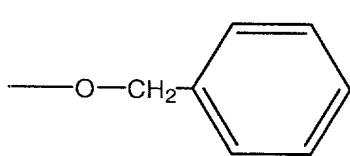
25

5 m is an integer of 1 to 6;  
v is an integer of 1 to 4;  
R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

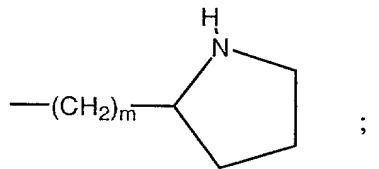
R<sup>7</sup> is H or



10 R<sup>8</sup> is selected from alkyl of 1 to 10 carbon atoms, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>H,



and

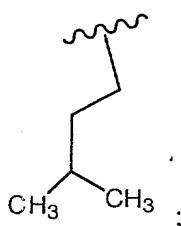


15

with the proviso that n is not 1 when

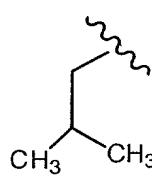
R<sup>1</sup> is H or CH<sub>3</sub>O-;

R<sup>2</sup> is H or

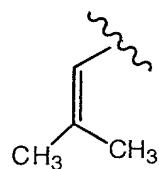


20

R<sup>3</sup> is



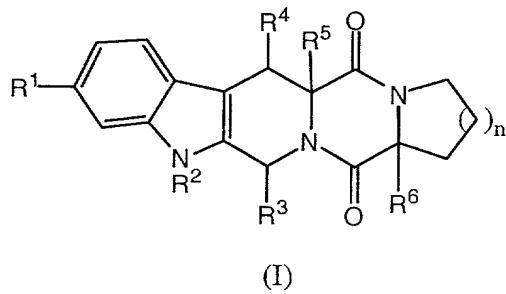
or



; and

25 R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;  
or a pharmaceutically acceptable salt thereof.

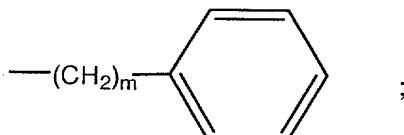
57. The method according to claim 13 wherein the chemosensitizing reversal agent is selected from a compound having the Formula (I)



5

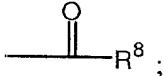
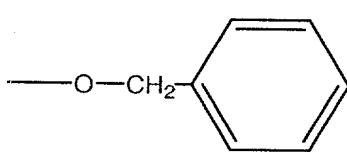
wherein:

n is an integer of 0, 1, or 2;

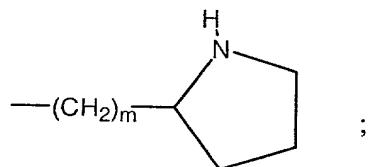
R<sup>1</sup> is hydrogen or alkoxy of 1 to 10 carbon atoms;10 R<sup>2</sup> is hydrogen or alkenyl of 2 to 10 carbon atoms;R<sup>3</sup> is hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms,R<sup>7</sup>NH(CH<sub>2</sub>)<sub>v</sub>- or

15 m is an integer of 1 to 6;

v is an integer of 1 to 4;

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;R<sup>7</sup> is H or20 R<sup>8</sup> is selected from alkyl of 1 to 10 carbon atoms, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>H,

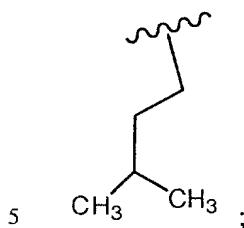
and



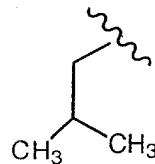
25

with the proviso that n is not 1 when

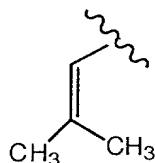
R<sup>1</sup> is H or CH<sub>3</sub>O-;R<sup>2</sup> is H or



R<sup>3</sup> is



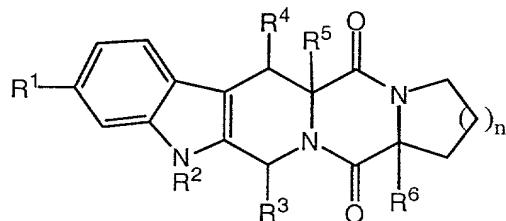
or



; and

10      R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;  
or a pharmaceutically acceptable salt thereof.

15      58. The method according to claim 18 wherein the chemosensitizing reversing agent is  
selected from a compound having the Formula (I)



(I)

wherein:

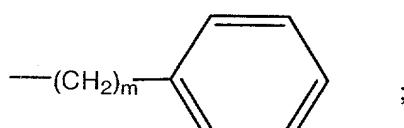
n is an integer of 0, 1, or 2;

20      R<sup>1</sup> is hydrogen or alkoxy of 1 to 10 carbon atoms;

R<sup>2</sup> is hydrogen or alkenyl of 2 to 10 carbon atoms;

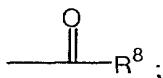
R<sup>3</sup> is hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms,

R<sup>7</sup>NH(CH<sub>2</sub>)<sub>v</sub> or



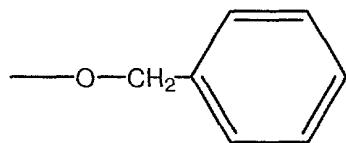
m is an integer of 1 to 6;

5    v is an integer of 1 to 4;  
R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;  
R<sup>7</sup> is H or

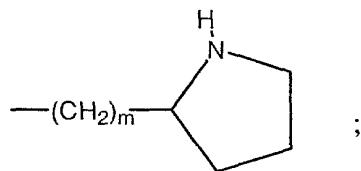


R<sup>8</sup> is selected from alkyl of 1 to 10 carbon atoms, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>H,

10

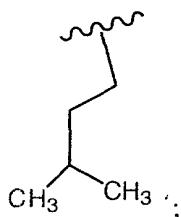


and



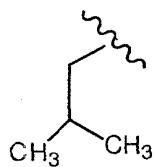
;

15    with the proviso that n is not 1 when  
R<sup>1</sup> is H or CH<sub>3</sub>O-;  
R<sup>2</sup> is H or

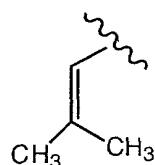


20

R<sup>3</sup> is



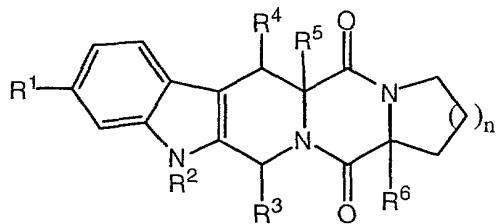
or



; and

25    R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;  
or a pharmaceutically acceptable salt thereof.

59. The method according to claim 24 wherein the chemosensitizing reversal agent is selected from a compound having the Formula (I)



(I)

5

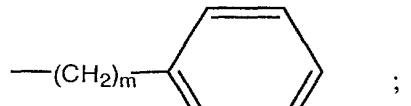
wherein:

n is an integer of 0, 1, or 2;

R<sup>1</sup> is hydrogen or alkoxy of 1 to 10 carbon atoms;

10 R<sup>2</sup> is hydrogen or alkenyl of 2 to 10 carbon atoms;

R<sup>3</sup> is hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms,  
R<sup>7</sup>NH(CH<sub>2</sub>)<sub>v</sub>- or

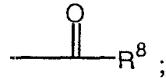


15 m is an integer of 1 to 6;

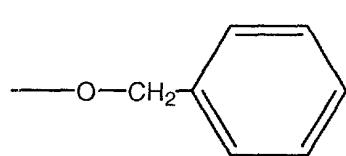
v is an integer of 1 to 4;

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

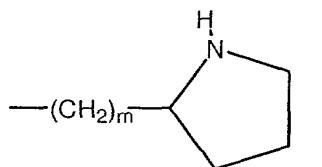
R<sup>7</sup> is H or



20 R<sup>8</sup> is selected from alkyl of 1 to 10 carbon atoms, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>H,



and

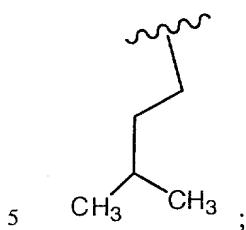


25

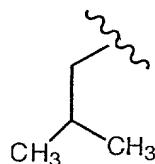
with the proviso that n is not 1 when

R<sup>1</sup> is H or CH<sub>3</sub>O-;

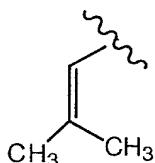
R<sup>2</sup> is H or



R<sup>3</sup> is



or

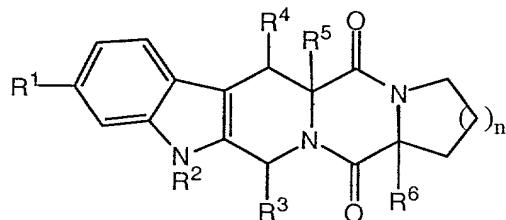


and

10 R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

or a pharmaceutically acceptable salt thereof.

15 60. The method according to claim 29 wherein the chemosensitizing reversal agent is selected from a compound having the Formula (I)



(I)

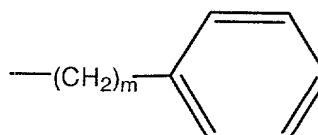
wherein:

n is an integer of 0, 1, or 2;

20 R<sup>1</sup> is hydrogen or alkoxy of 1 to 10 carbon atoms;

R<sup>2</sup> is hydrogen or alkenyl of 2 to 10 carbon atoms;

R<sup>3</sup> is hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms, R<sup>7</sup>NH(CH<sub>2</sub>)<sub>v</sub>- or



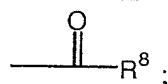
;

25

m is an integer of 1 to 6;

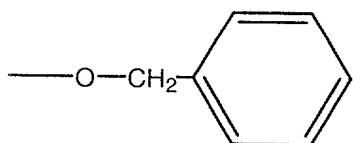
5 v is an integer of 1 to 4;  
R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

R<sup>7</sup> is H or

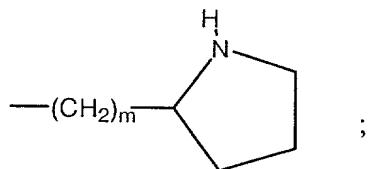


R<sup>8</sup> is selected from alkyl of 1 to 10 carbon atoms, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>H,

10



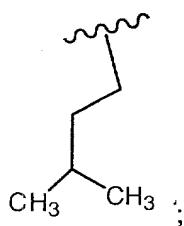
and



15 with the proviso that n is not 1 when

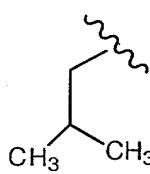
R<sup>1</sup> is H or CH<sub>3</sub>O-;

R<sup>2</sup> is H or

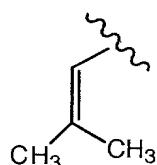


20

R<sup>3</sup> is



or

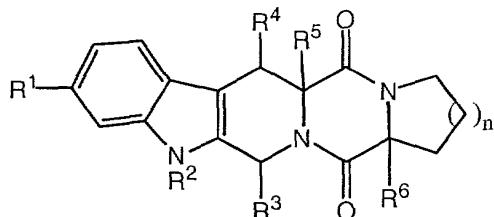


; and

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

25 or a pharmaceutically acceptable salt thereof.

61. The method according to claim 34 wherein the chemosensitizing reversal agent is selected from a compound having the Formula (I)



(I)

5

wherein:

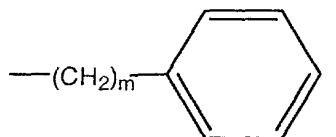
n is an integer of 0, 1, or 2;

R<sup>1</sup> is hydrogen or alkoxy of 1 to 10 carbon atoms;

10 R<sup>2</sup> is hydrogen or alkenyl of 2 to 10 carbon atoms;

R<sup>3</sup> is hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms,

R<sup>7</sup>NH(CH<sub>2</sub>)<sub>v</sub>- or

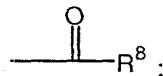


15 m is an integer of 1 to 6;

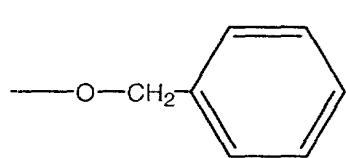
v is an integer of 1 to 4;

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

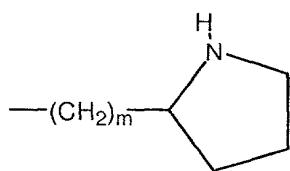
R<sup>7</sup> is H or



20 R<sup>8</sup> is selected from alkyl of 1 to 10 carbon atoms, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>H,



and

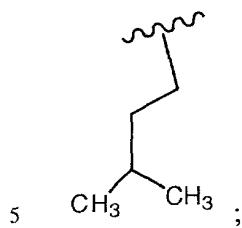


25

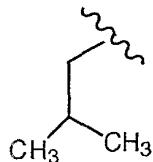
with the proviso that n is not 1 when

R<sup>1</sup> is H or CH<sub>3</sub>O-;

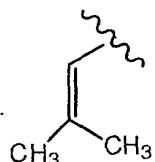
R<sup>2</sup> is H or



$R^3$  is



or



;

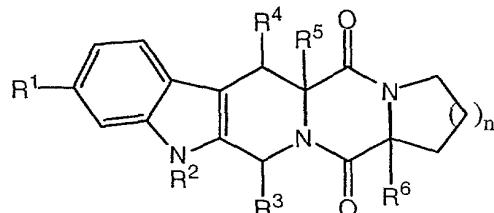
and

10

$R^4$ ,  $R^5$  and  $R^6$  are hydrogen;  
or a pharmaceutically acceptable salt thereof.

15

62. The method according to claim 39 wherein the chemosensitizing reversal agent is selected from a compound having the Formula (I)



(I)

wherein:

$n$  is an integer of 0, 1, or 2;

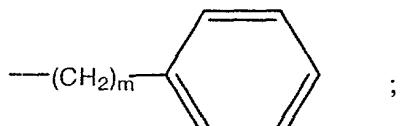
20  $R^1$  is hydrogen or alkoxy of 1 to 10 carbon atoms;

$R^2$  is hydrogen or alkenyl of 2 to 10 carbon atoms;

$R^3$  is hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms,

$R^7NH(CH_2)^v-$  or

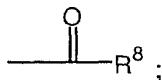
25



$m$  is an integer of 1 to 6;

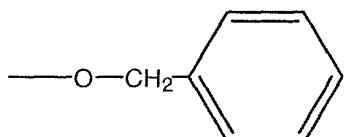
5 v is an integer of 1 to 4;  
R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

R<sup>7</sup> is H or

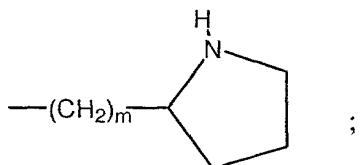


R<sup>8</sup> is selected from alkyl of 1 to 10 carbon atoms, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>H,

10



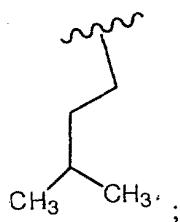
and



15 with the proviso that n is not 1 when

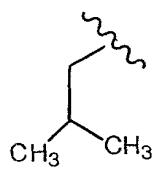
R<sup>1</sup> is H or CH<sub>3</sub>O-;

R<sup>2</sup> is H or

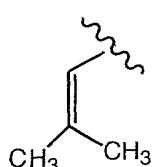


20

R<sup>3</sup> is



or



; and

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen;

25 or a pharmaceutically acceptable salt thereof.

63. A culture of the organism *Aspergillus fumigatus* having the identifying characteristics of LL-S266, said culture being capable of producing Fumitremorgin A, B and C in recoverable quantity upon fermentation in an aqueous nutrient medium containing  
30 assimilable sources of carbon and nitrogen.